

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

**ALKERMES, INC. and ALKERMES
PHARMA IRELAND LIMITED,**

Plaintiffs,

v.

TEVA PHARMACEUTICALS USA, INC.,

Defendant.

Civil Action No. 20-12470 (MCA)(MAH)

Filed Electronically

**CONTAINS HIGHLY CONFIDENTIAL
INFORMATION**

FILED UNDER SEAL

TEVA'S PRE-TRIAL BRIEF

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TABLE OF ABBREVIATIONS

'499 Patent	U.S. Patent No. 7,919,499
Alkermes	Collectively, Plaintiffs Alkermes, Inc. and Alkermes Pharma Ireland Limited
ANDA	Abbreviated New Drug Application
AUC	Area Under the Curve
Bartus Tr.	January 6, 2022 transcript of the videotaped deposition of Raymond Bartus, Ph.D. (excerpts attached as Exhibit 3 to the Declaration of Liza M. Walsh In Support Of Teva's Pre-Trial Brief, filed concurrently herewith)
DTX	Exhibit listed on Teva's Trial Exhibit List (D.I. 165 at 298–326)*
Ehrich Tr.	January 18, 2022 transcript of the videotaped deposition of Elliot Ehrich, M.D. (excerpts attached as Exhibit 4 to the Declaration of Liza M. Walsh In Support Of Teva's Pre-Trial Brief, filed concurrently herewith)
FDA	Food and Drug Administration
IPR	<i>Inter Partes</i> Review
Kerrigan Tr. Vol. 1	May 2, 2022 transcript of the videotaped deposition of James H. Kerrigan (excerpts attached as Exhibit 1 to the Declaration of Liza M. Walsh In Support Of Teva's Pre-Trial Brief, filed concurrently herewith)
Kerrigan Tr. Vol. 2	May 3, 2022 transcript of the videotaped deposition of James H. Kerrigan excerpts attached as Exhibit 2 to the Declaration of Liza M. Walsh In Support Of Teva's Pre-Trial Brief, filed concurrently herewith)
Patent Office	United States Patent and Trademark Office
PLA	Polylactic Acid
PLGA	Poly lactide-co-glycolide
PTAB	The Patent Trial and Appeal Board
PTX	Exhibit listed on Alkermes's Trial Exhibit List (D.I. 165 at 275–294)*

Teva	Defendant Teva Pharmaceuticals USA, Inc.
Weiss Tr.	May 25, 2022 transcript of the videotaped deposition of Roger D. Weiss, M.D. (excerpts attached as Exhibit 5 to the Declaration of Liza M. Walsh in support of Teva's Pre-Trial Brief, filed concurrently herewith)

* The parties will be providing the Court with a full set of electronic copies of the trial exhibits listed on the parties' respective trial exhibit list before the start of trial. Teva is happy to further provide the Court with paper copies of the specifically cited exhibits herein should the Court prefer.

Alkermes markets a long-acting, injectable form of naltrexone called Vivitrol. Vivitrol uses a 380-mg dose of naltrexone embedded in tiny plastic microspheres of a specific polymer (PLGA) that releases naltrexone slowly over time to treat patients suffering from alcohol or opioid dependence. But Alkermes did not invent naltrexone, or the use of naltrexone to treat addiction, or the PLGA polymer used to deliver the drug. In fact, naltrexone has been FDA-approved as a safe and effective treatment for addiction since the 1980s, and the PLGA delivery system has been known since at least 1984. Long-acting formulations of naltrexone are generally desirable for addiction treatment because addicts on short-acting oral naltrexone who want to become intoxicated can simply refrain from taking their naltrexone before consuming opioids or alcohol. For that reason, PLGA polymers that slowly release the naltrexone were an attractive option for developing a long-acting product. Indeed, by 2001—years before the '499 patent and Vivitrol—a company called BioTek had successfully developed a long-acting naltrexone-PLGA formulation called Depotrex, administered it in a 384 mg dose, and publicly announced its product as a safe and effective addiction treatment.

Alkermes obtained U.S. Patent No. 7,919,499 (the '499 patent) to protect its monopoly on Vivitrol. Claims 1–13 are asserted against Teva in this case. Claim 1 is illustrative:

1. A method for treating an individual in need of naltrexone comprising the step of parenterally administering a long acting formulation comprising about 310 mg to about 480 mg of naltrexone and a biocompatible polymer to the individual wherein the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration and wherein the biocompatible polymer is a polylactide-co-glycolide [PLGA] polymer.¹

Recognizing that the claimed long-acting naltrexone formulation was nothing new over what

¹ Dependent claims 2–13 further specify that the dose is “about 380 mg” and the formulation has an “about 3.3 times greater” AUC, the concentration of naltrexone in the formulation, the time periods for administration and related release of naltrexone for the formulation, the use of the formulation to treat alcohol dependence, or other conditions of administration. DTX-001.0017.

BioTek and others in the field had done before, Alkermes did not point to the use of naltrexone, the dose, or the PLGA polymer formulation when it told the Patent Office what the allegedly novel features of the claimed invention were over what was disclosed in the prior art. Instead, it pointed *only* to the claim limitation “wherein the serum AUC of naltrexone is about three times greater than that achieved by 50 mg/day oral administration.” “AUC” refers to the area under the curve of a graph plotting the concentration of a drug in a patient’s blood as a function of time. Thus, it measures the total amount of drug present in the bloodstream over some amount of time (also referred to as the overall “exposure” to the drug). That is, Alkermes obtained its patent by asserting that the overall exposure to naltrexone in its injectable PLGA formulation was about three times greater than that achieved by 50 mg/day of oral naltrexone. But this seemingly straightforward comparison—long-acting injected AUC is about three times greater than oral AUC—turns out to be very confusing in practice. For example, AUC for naltrexone taken orally varies greatly from patient to patient, depending on how much of the drug is metabolized by the liver before it enters the general circulation. Which oral AUC should one use? Additionally, how many 50-mg/day doses should one use for the comparison to a single injected dose? Just a single day? Multiple days? The patent does not say. Remarkably, the patent specification contains *no* AUC data at all.

Thus, the resulting claims are invalid on three separate grounds. *First*, the claims are indefinite because there are a number of equally valid ways to measure AUC, but the ’499 patent does not provide any guidance on which oral AUC to use or over what time period the AUC comparison between injected and oral naltrexone should be made. A given formulation could fall inside the scope of the claims if the comparison is done one way but outside the claims if the comparison is done another way. As a result, a party desiring to avoid infringement might not be

able to tell whether it had succeeded. Because the patent does not inform the public with sufficient definiteness how to distinguish formulations falling within the claims from those falling outside the claims, the claims are invalid. *Infra*, Part I. *Second*, even if one were to ignore the indefiniteness problem and focus on the AUC data that Alkermes presented to the Patent Office during prosecution, the claims would still be invalid as obvious because putting naltrexone in a PLGA polymer to produce a long-lasting formulation for addiction treatment is an obvious thing to do—in fact, BioTek had already done so in its Depotrex product—and the pertinent AUC profile is an inherent property of such naltrexone-PLGA formulations. *Infra*, Part II. Further, none of the secondary considerations pertaining to non-obviousness that Alkermes invokes is sufficient to demonstrate non-obviousness in the face of Teva’s strong *prima facie* case of obviousness. *Infra*, Part III. *Third*, if Alkermes were to argue that the pertinent AUC profile is not an inherent property of naltrexone-PLGA formulations and instead is the result of something special in Alkermes’s own formulation or technique, then the patent would be invalid for lack of written description because it does not disclose what that something special is, and so it does not demonstrate that the inventor had possession of the mysterious something special. *Infra*, Part IV. Accordingly, Teva respectfully submits that, after hearing the evidence at trial, the Court should enter judgment that all of the asserted claims are invalid.

BACKGROUND

ALL FEATURES OF THE CLAIMED INVENTION ARE IN THE PRIOR ART

Alcohol and opioid dependence are chronic diseases that affect millions of people in the United States, and it has been understood for many decades that these diseases often require medication to treat. Because naltrexone blocks the opioid receptors in the brain, reducing cravings and feelings of euphoria associated with alcohol and opioid consumption, it was an obvious choice for such a medication. It was also an obvious choice to administer naltrexone via

a long-acting, injectable formulation because it increases patient compliance (since the patient does not have to remember to take the medication on a daily basis) and also allows for sustained levels of the drug in the patient's bloodstream during the course of treatment. In fact, years before Alkermes created its own formulation, others in the field created a long-acting naltrexone formulation that utilized the same doses of naltrexone in the same PLGA delivery system and demonstrated the same AUC characteristics as the claimed formulation (when calculated using the inventor's AUC methodology). These developments in the field years before the '499 patent demonstrate that the so-called invention of the asserted claims was really no invention at all.

A. Naltrexone was available for decades before the '499 patent

Naltrexone has a long clinical history of successfully treating addiction. Naltrexone was approved by the FDA to treat opioid and alcohol dependence in 1984 and 1994, respectively. Further, many years prior to the April 22, 2004 filing date of the '499 patent application, the prior art and at least a dozen randomized, controlled trials confirmed the overall clinical effectiveness, safety, and tolerability of long-term oral naltrexone therapies for treating diseases like alcoholism. *E.g.*, DTX-133. Accordingly, both before 2004 and also today, naltrexone has been one of the most widely used treatments for addiction. *E.g.*, DTX-196.0003; DTX-197.0009–10. In fact, Alkermes's own expert confirmed that, prior to 2004, naltrexone was reported to be generally well tolerated by patients and was one of the most promising medications to treat addiction. Weiss Tr. at 96:14–21, *id.* at 14:13–15:4.

B. Others successfully developed long-acting naltrexone formulations years before the '499 patent

Despite the reported clinical benefits and overall safety and tolerability of oral naltrexone therapy, it was also understood before 2004 that orally administered naltrexone had certain drawbacks. First, naltrexone is subject to a significant and highly variable “first-pass effect”—

i.e., the elimination of an active ingredient by the liver before it enters systemic circulation—which causes a high level of variability in naltrexone blood plasma concentrations in subjects following oral administration. Second, and most importantly, oral naltrexone users often failed to take their daily medications, thus reducing the overall efficacy of the treatment.

In order to solve these issues, well before April 22, 2004, various entities had worked on developing long-acting, injectable dosage forms of naltrexone that were not subject to the first-pass effect and only had to be taken about once a month. As early as 1984 and 1985, researchers recognized the need for “improving patient compliance” for oral naltrexone and so developed an injectable, sustained-release dosage form using a polymer delivery system that released 63 mg naltrexone over a one-month period. DTX-130.0002 (Chiang 1985); DTX-131.0001 (Chiang 1984). While that formulation demonstrated that the “sustained-release dosage form [] can be clinically useful,” it failed to achieve plasma levels close to therapeutic levels (about 2 ng/ml²) for the one-month period. DTX-130.0007. Thus, the researchers suggested “future development” of doses “greater than 63 mg” to “maintain clinically-effective” plasma levels. *Id.*

One of the first companies to undertake the “future development” recommended by Chiang was BioTek. In 1987, BioTek began development of an injectable formulation, which it ultimately named Depotrex, that utilized PLGA polymer microspheres to slowly release the naltrexone. Kerrigan Tr. Vol. 1 at 29:14–30:10; DTX-073.0001; DTX-215.0018, 0021. By the late 1990s, researchers working with Depotrex published papers regarding doses ranging from 52 mg to 206 mg, concluding that they were safe and well-tolerated with minimal side effects, and that they had an important place for addiction by addressing the well-known patient-compliance issues with oral naltrexone. *See* DTX-216 (Heishman); DTX-124 (Alim); DTX-217 (Kranzler).

² DTX-213.0012 (Verebey, 1980) (“in therapy for effective opiate antagonistic activity, plasma levels of 2.0 ng/ml or greater should be maintained”).

However, these researchers also recommended further studies on the Depotrex formulation, including to evaluate “higher doses to achieve a sustained naltrexone plasma concentration of 1–2 ng/ml.” DTX-216.0003; *see also* DTX-124.0003 (recommending further study); DTX-217.0005 (same).

In November 2000, a researcher working with BioTek, Dr. Sandra Comer, evaluated Depotrex administered in a 384-mg dose and reported that: (a) the formulation achieved the previously suggested sustained naltrexone plasma concentrations of 1–2 ng/ml for at least about a month; (b) there were “no untoward side-effects”; and (c) it provided “safe, effective, [and] long-lasting” treatment for addiction that “could increase compliance and ultimately improve treatment effectiveness” over oral naltrexone therapy. DTX-132.0007, 0008, 0010–0011. Dr. Comer thus concluded that this “formulation of naltrexone that requires only once-a-month administration has important and exciting treatment implications.” *Id.* at 0015. Dr. Comer’s findings were then peer-reviewed and published in the renowned *Journal of Psychopharmacology* and published online and in print in November 2001 and February 2002, respectively. *Id.* at 0006–0007.

C. Alkermes’s own development of Vivitrol and the ’499 patent confirm that the claimed invention is nothing new

Alkermes’s development efforts for its own long-acting naltrexone formulation reveal that Alkermes failed to break any new ground but rather merely combined known prior-art elements using known techniques to achieve expected results. Alkermes publicly conceded in 2003 that: (a) it had been known for decades that naltrexone had “utility” in treating opioid and alcohol dependence; (b) it was also well known that oral naltrexone suffered from “poor adherence to the prescribed daily dosing schedule”; (c) accordingly, “the idea of developing an extended-release formulation of naltrexone” to address this patient-compliance issue “is not

novel”; and (d) a successful long-acting naltrexone formulation should target and maintain “plasma levels above the minimum therapeutic range [of] 2 ng/ml.” DTX-127.0001, 0007, 0008.

Alkermes’s development of Vivitrol closely mirrored BioTek’s development of Depotrex, but, importantly, each development step occurred *years after* BioTek’s. BioTek identified naltrexone as a candidate for a long-acting, injectable formulation in 1987; Alkermes did not do so until the mid-1990s. Kerrigan Tr. Vol. 1 at 29:14–30:10; Bartus Tr. 34:16–35:1. Biotech tested long-acting naltrexone formulations utilizing PLGA microspheres in humans as early as 1994; Alkermes did not begin its clinical trials using such formulations until 2000. DTX-216; Kerrigan Tr. Vol. 1 at 67:20–68:4; Ehrich Tr. at 23:21–24:6, 95:5–13. BioTek identified the 384-mg dose as an “exciting” treatment option providing therapeutic plasma levels for at least about a month by November 2000; Alkermes did not begin testing its 380-mg dose until February 2002, and did not complete its evaluation of the blood plasma levels for this formulation until November 2004. DTX-132; D.I. 165 at 30; DTX-002.0493. During development for Vivitrol, Alkermes was aware of the earlier-developed Depotrex and even considered acquiring the formulation. *E.g.*, DTX-0007.

The evidence shows the sole named inventor on the ’499 patent, Dr. Ehrich, did not himself choose the active ingredient, the dose, or the formulation of the claimed invention or Vivitrol. Dr. Ehrich freely admitted that it was not his idea to create a long-acting naltrexone formulation with a PLGA polymer delivery system; instead, others at Alkermes—who are *not* named as inventors on the ’499 patent—came up with that idea before he was even employed by Alkermes. Ehrich Tr. at 87:2–88:12. Alkermes also has not cited or produced a single document in this case indicating that Dr. Ehrich was the one who selected the claimed dose; to the contrary, the documents Alkermes has produced regarding the rationale for choosing the claimed dose

contain no mention of Dr. Ehrich. Further, when the Patent Office rejected the then-pending claims as obvious in view of prior art references disclosing PLGA and a 350-mg dose, Dr. Ehrich did not argue that these elements were, in fact, inventive. Instead, he submitted a sworn declaration to the Patent Office that pointed *only* to a post-filing Alkermes clinical trial report reflecting that the claimed formulation had the purportedly “unexpected” AUC profile with about three times the exposure of 50 mg of oral naltrexone. DTX-002.0493–511 (citing the ALK21-005 clinical trial final report). The asserted claims issued without any further rejections in view of the prior art. *Id.* at 0512–705.

Curiously, the AUC profile in the claims is entirely unsupported by the specification of the '499 patent, which contains *no disclosure* regarding blood serum or AUC data for either oral or long-acting naltrexone formulations, or any methods for obtaining such AUC data. The only Alkermes clinical trial data mentioned in the specification is for the ALK21-003 clinical trial that did not measure the AUC of any formulation. *See* D.I. 165 at 19. The ALK21-005 clinical trial cited in Dr. Ehrich’s declaration to the Patent Office as allegedly demonstrating the “unexpected” AUC properties of the claims is not mentioned in the patent specification at all. *Id.* Furthermore, Dr. Ehrich’s data submitted in his post-filing declaration fails to differentiate that formulation from the prior art. When using the same AUC value for oral naltrexone and the same measured time period that Dr. Ehrich used in his declaration, the 384-mg dose of BioTek’s prior-art Depotrex product exhibited *the exact same* AUC properties as the claimed formulation when compared to oral naltrexone.

The claimed AUC profile does not save the claims from invalidity, as discussed below.

ARGUMENT

I. The asserted claims are invalid as indefinite because they do not adequately inform the public regarding the scope of Alkermes’s property rights

A patent is a property right granted by the government to the patent owner. The claims of a patent define the scope of this property right, and thus, 35 U.S.C. § 112 requires that the inventor must draft the claims so that “it may be known which features may be safely used or manufactured without a license and which may not.” *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 369 (1938); *see also Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722, 730–31 (2002). Where a claim fails to “inform, with reasonable certainty, those skilled in the art about the scope of the invention,” the claim is invalid as indefinite under § 112. *Nautilus, Inc. v. Biosig Inst., Inc.*, 572 U.S. 898, 901 (2014). A specific example of this is where the claim language “might mean several different things,” causing the same item to fall both inside and outside the scope of the claims depending on the definition used, yet the patent provides “no informed and confident choice” about which definition to select. *HZNP Meds. LLC v. Actavis Labs UT, Inc.*, 940 F.3d 680, 697, 698 (Fed. Cir. 2019); *see also Dow Chem. Co. v. Nova Chems. Corp.*, 803 F.3d 620, 630 (Fed. Cir. 2015) (where a claim recites achievement of a certain result, the patent “must disclose a single known approach or establish that, where multiple known approaches exist, a person having ordinary skill in the art would know which approach to select . . . [p]articularly this is so where different approaches to measurement are involved.”). Alkermes’s asserted claims fail for exactly this reason.

As discussed above, given the clear teachings of the prior art showing that the formulation recited in the asserted claims was nothing new, Alkermes included and emphasized the additional limitation that the claimed formulation achieves an AUC about three times greater than that of 50 mg/day of oral naltrexone. *See* DTX-002.0485. Making sense of this limitation is

harder than it may at first appear, however, for there are many ways to measure the AUC of both the injectable, long-acting formulation and the AUC of oral naltrexone, and the patent fails to provide “an informed and confident choice” about which measurements to use—indeed, the patent specification says nothing whatsoever about AUC. The AUC of a long-acting naltrexone formulation will have a different value depending on the length of time that the AUC—or area under the curve—is integrated, and this value may change dramatically with the addition or subtraction of only a few days within that time interval, causing the ratio between the AUC of the long-acting naltrexone formulation as compared to oral naltrexone to similarly change dramatically. Yet neither the claims nor specification of the ’499 patent provides *any* guidance regarding what time interval to use for calculating the AUC (indeed, the specification contemplates using time intervals of a week, two weeks, three weeks, or four weeks or even longer, *see* DTX-001.0008 at 3:60–64). Thus, the exact same formulation could demonstrate AUC properties that simultaneously fall inside and outside the scope of the claims depending purely on the time interval selected for calculating such properties.

Furthermore, because oral naltrexone is subject to a significant first-pass effect, discussed above, for any given study, day, or subject, the AUC for “50 mg/day oral administration” of naltrexone will vary greatly. Yet neither the claims nor the specification of the ’499 patent provides *any* guidance regarding what oral AUC value or values to select or what methodology to use to calculate such a value. And the length of the time period for comparison is important for measuring the oral AUC as well, since if the measurement period is one day, a 50-mg/day dose would be just 50 mg, while if the measurement period is 30 days, then 50 mg/day entails administering a total of 1500 mg of oral naltrexone. Again, the same long-acting naltrexone could fall both in and outside the scope of the claims based solely on what AUC value is selected

for orally administered naltrexone and how long of a period is used for the comparison.

Accordingly, a competitor who wanted to create a long-acting, injectable naltrexone formulation comprising PLGA and about a 380-mg dose of naltrexone—which is all within the prior art—would have no way of knowing whether that formulation fell within or outside of the claims. For example, the serum data provided in the Comer reference shows that the AUC for the 384-mg dose of Depotrex falls inside the scope of the claims when using the exact value for oral AUC and the exact measured time period selected by Dr. Ehrich in his declaration (but not disclosed anywhere in the '499 patent itself). If, however, any other value for oral AUC or any other measured time periods are selected, then the ratio of the AUC for the exact same long-acting naltrexone formulation to that of 50 mg/day oral naltrexone will change and can fall outside the scope of the asserted claims. Thus, the asserted claims violate the legal requirement that they clearly apprise the public of the scope of Alkermes's property right. *Dow Chem.*, 803 F.3d at 634 (finding claims requiring calculating slope of strain hardening indefinite because there were three known methods for calculating the slope, each resulting in a different value, and so the specific method chosen “could affect whether or not a given product infringes the claims,” yet the patent failed to provide “any guidance as to which method should be used”).

Alkermes has suggested that the claims are not indefinite because those skilled in the art would simply know to use the same methodology and values that Dr. Ehrich used in his declaration to the Patent Office to determine AUC: namely, by conducting a pharmacokinetic study evaluating the AUC of both long-acting and oral naltrexone in the same group of healthy individuals over the course of one month. That suggestion finds no support in the patent itself since Dr. Ehrich's post-filing data and methodology are mentioned nowhere in the specification or claims. The suggestion also contradicts the plain text of the claims, which recite administering

the claimed formulation to “*an individual in need of naltrexone*” rather than to a group of healthy individuals. Indeed, the Federal Circuit has held that reading such a requirement from the prosecution history into the claims where it directly contradicts the specification and claim language is inappropriate. *HTC Corp. v. IPCom GmbH & Co., KG*, 667 F.3d 1270, 1276 (Fed. Cir. 2012) (finding argument that the claim scope should be dictated by patent owner’s statements made during prosecution “unpersuasive when weighed against the plain language of the claims and the specification”). Dr. Ehrich’s declaration thus cannot save the claims from being indefinite.

II. The asserted claims are all invalid as obvious in view of the prior art

Even if one ignores the indefiniteness problem with the claimed AUC profile, the claims are invalid because the claimed invention is simply an obvious combination of known, effective amounts of an old drug delivered using a known delivery system to achieve known, effective blood serum concentrations.

Teva expects that Alkermes will rely on three main arguments to resist the conclusion of obviousness: *first*, selection of the claimed naltrexone therapy was not obvious because persons of skill in the art would have viewed any benefit to such a therapy to be outweighed by its drawbacks, such as risk of certain adverse effects; *second*, the Depotrex-related prior art cannot invalidate the claims because: (a) the Depotrex formulation was never given in a *single injection* of 384 mg (instead, Dr. Comer gave it in two injections of 192 mg in the same procedure), and (b) the Depotrex product was “secret” and thus should not be considered prior art at all; and *third*, that secondary considerations of non-obviousness, such as Vivitrol’s alleged clinical benefits and success over prior treatments, show that the claimed invention was non-obvious. Alkermes is wrong on all three points.

First, any suggestion that a skilled artisan would not select naltrexone therapy for

development due to purported drawbacks is flatly contradicted by the simple fact that skilled artisans, like those working at BioTek, *did* select long-acting naltrexone therapy using the claimed doses and PLGA delivery system to achieve the claimed AUC properties. Moreover, even if there had been a serious concern about such drawbacks (there was not), such a concern could not be used to support Alkermes's assertions of non-obviousness because the claimed invention suffers from those very same drawbacks and hence did not resolve the concern.

Second, the Depotrex-related prior art does indeed invalidate the asserted claims. Alkermes's argument that Comer administered two injections rather than one is a distinction without a difference. On their face, the claims do not require that the total claimed dose be given in a single injection (or that the oral dose be given in a single tablet) but rather require only that the dose be given in a single administration step. Just as swallowing two 200 mg tablets of ibuprofen to treat a headache constitutes a single administration of 400 mg ibuprofen, Dr. Comer's two injections of 192 mg naltrexone, one in each buttock during a single procedure, constituted a single administration of 384 mg naltrexone. Thus, the claims plainly cover Dr. Comer's administration of the 384 mg dose of Depotrex, which inherently results in the claimed AUC properties.

With respect to Depotrex's purported secrecy, Alkermes's assertions are plainly contradicted by BioTek's actions, as it not only provided Depotrex to researchers who published their findings regarding Depotrex in publicly available papers but also detailed the specific components and AUC properties of Depotrex in the Nuwayser patent, filed in 2002.

Third, Alkermes cannot establish the legally required nexus showing Alkermes's cited secondary considerations regarding Vivitrol stem from the novel AUC features of the claimed invention, as opposed to what was already known in the prior art or other extraneous factors.

These indicia taken as a whole fail to overcome the strong *prima facie* showing of obviousness that Teva expects to make at trial. Thus, as explained below, the claims are invalid as obvious.

A. Claims reciting administration of a formulation and achievement of a result are invalid as obvious where the prior art discloses the formulation, and achievement of the result flows inherently from administration

The Supreme Court has emphasized that “[g]ranting patent protection to [obvious] advances that would occur in the ordinary course without real innovation retards progress.” *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 419 (2007). Accordingly, under 35 U.S.C. § 103, a patent claim is invalid for obviousness if a person having ordinary skill in the art “would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success in doing so.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (2007); *see also KSR*, 550 U.S. at 422.

One specific application of these principles in the pharmaceutical space occurs where a patent claim recites a specific formulation that was already disclosed in or obvious from the prior art and then adds a requirement that the formulation exhibit certain properties following administration. When these properties are an inherent or natural result of administering the claimed formulation, their inclusion in the claims cannot render the claims non-obvious. *Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1190 (Fed. Cir. 2019) (“ . . . ‘obvious formulation cannot become non-obvious simply by administering it to a patient and claiming the resulting serum concentrations,’ because ‘[t]o hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property’”); *King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1275–76 (Fed. Cir. 2010) (similar); *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1332–33 (Fed. Cir. 2020) (similar). The asserted claims are invalid as obvious for this exact reason. Others in the field already created the long-acting formulation of the claims to provide a once-a-month

treatment for addiction, and the additional AUC limitations cannot save the claims because they simply recite a property that is an inherent result of administration.

At trial, Teva expects to present two prior-art combinations, either of which suffices on its own to invalidate the asserted claims.

B. All asserted claims are invalid as obvious in view of Depotrex and related patents and publications

Teva will demonstrate that all asserted claims are obvious in light of the combination of either Comer, Nuwayser, and Leavitt, or alternatively, the Depotrex product, Comer, Nuwayser, and Leavitt, as described below.

Comer: As noted above, Dr. Sandra Comer’s peer-reviewed article entitled “Depot naltrexone: long-lasting antagonism of the effects of heroin in humans” in the *Journal of Psychopharmacology* was published online on November 1, 2001, and in print in February 2002. DTX-132. Comer reports treating patients with a single administration of either one or two injections of Depotrex at total strengths of 192 and 384 mg naltrexone, respectively, and further reports that the 384-mg dose provided therapeutic naltrexone plasma levels above 1–2 ng/ml for about a month and also resulted in a plasma AUC of about three times greater than the plasma AUC of 50 mg/day of oral naltrexone (when using the same AUC value for oral naltrexone and the same measured time period that Dr. Ehrich used in his declaration). *Id.* at 0007, 0010. Dr. Comer concluded that Depotrex was a “safe, effective” and “exciting” treatment for addiction, with the potential for only once-a-month administration. *Id.* at 0007, 0014, 0015.

Nuwayser: Although Comer does not disclose the specific makeup of Depotrex (other than the dose), BioTek publicly described the components of Depotrex, along with methods for its manufacture and use, in a patent application filed on May 31, 2002, which ultimately issued

as U.S. Patent No. 7,157,102 to Elie Nuwayser (“Nuwayser”).³ DTX-215. Dr. Nuwayser was a co-author of the Comer reference. DTX-132.0007. Nuwayser describes the methods of making the PLGA microspheres for Depotrex containing naltrexone and using Depotrex to treat addicts. DTX-215.0021. Nuwayser also discloses the same AUC data provided in Comer. *Id.* at Fig. 7.

Depotrex product: The Comer and Nuwayser references describe Depotrex in detail, and BioTek shared Depotrex with researchers, Kerrigan Tr. Vol. 1 at 77:19–78:15, and permitted them to publicly disclose their findings in, for example, the Heishman, Alim, Kranzler, and Comer papers discussed above. *Supra*. These published findings included Dr. Comer’s paper showing that the 384-mg dose would inherently result in a plasma AUC of about three times greater than that provided by 50 mg/day of orally administered naltrexone (when using Dr. Ehrich’s AUC methodology). BioTek publicly confirmed this by publishing the exact same data—along with the specific components of Depotrex—within its Nuwayser patent. *Supra*. The evidence will also show that BioTek’s own internal testing confirmed Depotrex’s AUC properties as described in Comer and Nuwayser. *Hospira*, 946 F.3d at 1329–30 (“[e]xtrinsic evidence can be used to demonstrate what is ‘necessarily present’ in a prior art embodiment” even if it “is not itself prior art”). Accordingly, Depotrex, including the use of the 384-mg dose, and the resulting AUC, was publicly available well before April 22, 2004, and is prior art to the asserted claims. *UCB, Inc. v. Watson Labs Inc.*, 927 F.3d 1272, 1290–91 (Fed. Cir. 2019) (patient’s use of a pharmaceutical that necessarily contained the claimed crystal qualified as a public use); *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1305–06 (Fed. Cir. 2006) (prior product as used in doctor’s practice and described in documents disseminated at seminars

³ Because the Nuwayser patent application was filed approximately two years before the April 22, 2004 invention date of the asserted claims, the Nuwayser patent qualifies as prior art under 35 U.S.C. § 102(e). *See* D.I. 181 at 2.

qualified as prior art).

Leavitt: In March 2002, an article was published in the Addiction Treatment Forum Journal, with editor Stewart B. Leavitt, Ph.D., entitled “Evidence for the Efficacy of Naltrexone in the treatment of Alcohol Dependence (Alcoholism).” DTX-133. Leavitt summarizes fourteen randomized, controlled clinical trials regarding oral naltrexone and concludes that naltrexone was a clinically effective treatment for addiction (such as alcoholism) and was safe and tolerable, with long-term therapy of more than six months potentially being most effective. *Id.* at 0003, 0007.

A skilled artisan would understand the first-pass effect and patient-compliance issues stemming from oral naltrexone, discussed above, and would be motivated to create a long-acting naltrexone formulation to solve these problems. *Cross Med. Products, Inc. v. Medtronic Sofamor Danek Inc.*, 424 F.3d 1293, 1322 (Fed. Cir. 2005) (“[e]vidence that a person of ordinary skill in the art recognized the same problem to be solved as the inventor and suggested a solution is, at the least, probative of a person of ordinary skill in the art’s willingness to search the prior art in the same field for a suggestion on how to solve that problem”). A skilled artisan would have seen from Comer that administration of the 384-mg dose of Depotrex achieved precisely these goals and was safe and effective. Such an artisan would conclude, as Comer did, that this treatment had “exciting” potential for a once-a-month addiction therapy. Such an artisan would also understand from Leavitt that it would be desirable to administer the 384-mg dose of Depotrex once-a-month for up to six to nine months for best treatment results.

The only element missing from Comer’s disclosure was the precise delivery system for Depotrex, but that would be easily remedied by looking to the publicly available Depotrex formulation itself or the Nuwayser reference, which discloses the PLGA and naltrexone contents

of Depotrex (including their concentrations) as well as the same inherent blood serum properties following administration described in Comer. Thus, the combination of either Comer, Nuwayser, and Leavitt, or alternatively, the Depotrex product, Comer, Nuwayser, and Leavitt easily provides a *prima facie* case that the patent claims are invalid as obvious.

C. The prior art does not teach away from selecting long-acting formulations using about 380 mg naltrexone and achieving claimed AUC properties

Alkermes will likely argue that the claims were not obvious because a person of ordinary skill in the art would have been dissuaded from creating the claimed long-acting naltrexone formulation because: (a) naltrexone itself was thought to be ineffective with unacceptable adverse effects; (b) long-acting, injectable naltrexone formulations were thought to have even more adverse effects than oral naltrexone; and (c) even if a skilled artisan was motivated to create a long-acting naltrexone formulation, the artisan would not use a dose and AUC exposure as high as the ones claimed in order to minimize these effects, but would instead target a dose of lower than the 206-mg dose in Kranzler and a naltrexone exposure comparable to once-daily oral naltrexone and less than 1 ng/ml. These arguments are contrary to the facts and the law.

First, the plain fact is that others in the field *did* combine the teachings of the prior art to create a long-acting formulation like the one claimed. *Supra*. Thus, Alkermes's assertion that a skilled artisan would not be motivated to combine these teachings to arrive at the claimed invention is "wholly undermin[ed]," and cannot rebut Teva's *prima facie* case of obviousness. *Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F. 4th 1354, 1369 (Fed. Cir. 2022) (rejecting no motivation to "select the specific combination" of claimed components where the prior art "provide[d] exemplary formulations comprising" these components); *I/P Engine, Inc. v. AOL Inc.*, 576 F. App'x. 982, 986 (Fed. Cir. 2014) (rejecting no motivation to combine where prior art "describ[ed] the advantages" of making the combination); *E.I. du Pont De Nemours and*

Co. v. MacDermid Printing Soln's, L.L.C., 657 F. App'x. 1004, 1014 (Fed. Cir. 2016) (similar).

Alkermes's arguments further run afoul of the legal principle that the teachings of the prior art, purportedly teaching away from creating the claimed invention, are *only* probative of non-obviousness where they *explicitly* “criticize, discredit, or otherwise discourage” a skilled artisan from following the path taken by the inventor. *SightSound Techs., LLC v. Apple Inc.*, 809 F.3d 1307, 1320 (Fed. Cir. 2015). Here, the evidence not only fails to show any sort of explicit criticism or discouragement from creating the claimed invention (as is legally required), but instead shows explicit *encouragement* to do so.

With respect to the alleged belief that naltrexone was not particularly effective, this is directly contradicted by the extensive evidence showing that naltrexone was FDA approved for treating addiction, and that a multitude of randomized, controlled trials confirmed its efficacy (as reported in Leavitt). *Supra*. Indeed, the *only* evidence Alkermes has cited that supposedly contradicts these findings is a single trial listed in Leavitt finding that a certain sub-group of older males had better outcomes with therapy than naltrexone. *See* DTX-133.0003 (citing the Krystal study). But this singular study cannot support an assertion of teaching away as Leavitt concludes it was an outlier with various quality issues, directly conflicted with the dozen other studies showing naltrexone *was* effective, and even with these limitations, a close review of the study's results still showed that naltrexone could provide a “significant benefit clinically.” *Id.* at 0005.

With respect to the purported adverse effects stemming from both oral and long-acting, injectable naltrexone treatment—such as potential liver injury, injection site reactions including reactions stemming from the larger injection volumes and needles required to administer an effective dose, inflammatory and allergic responses, and reduction in effective pain

management—these adverse effects cannot support a finding of teaching away or non-obviousness. The same prior art Alkermes cites reporting these potential adverse effects, including the Heishman, Alim, and Kranzler studies, discussed above, explicitly notes they were mild, and affirmatively recommends naltrexone treatments despite such events. *Supra*. And even if adverse effects were a significant concern (they were not), they do not support relevant teaching away because the evidence will show that the claimed long-acting formulation of the '499 patent did not solve these concerns either. *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1374 (Fed. Cir. 2005) (alleged teaching away from selecting higher dose due to side effects irrelevant as the patent did not “explain how its higher dosing would overcome these dose-related side-effects”).

Finally, with respect to Alkermes’s assertion that a skilled artisan would not select the claimed 310–480-mg dose or the 1–2-ng/ml naltrexone blood concentration—and instead would target a lower dose providing comparable exposure to oral naltrexone and blood concentrations of less than 1 ng/ml—in order to avoid adverse effects, this is again belied by the fact that the art, like Comer, specifically taught the use of such a higher dose to achieve such a higher naltrexone blood concentration. *Supra*. Nor does Alkermes’s reliance on the Kranzler study regarding the 206-mg dose of Depotrex show otherwise. Alkermes has argued Kranzler concluded that because even “minimal” naltrexone blood levels were effective, the study recommended *reducing* the 206-mg dose to avoid adverse effects. But this both mischaracterizes Kranzler (which shows the 206-mg dose only demonstrated naltrexone concentrations greater than 1 ng/ml for 21 days, and concluded the dose was “not ideal” under the criteria that it would, *inter alia*, last for 30 days), and also entirely ignores that Dr. Comer explicitly cited Kranzler in her paper, yet still selected a “high” dose of 384 mg of Depotrex that achieved at least 1–2-ng/ml concentrations for about a

month and found this dose was safe and well tolerated. DTX-217.0002–03, 0005; DTX-132.0008, 0010. It also ignores that Alkermes recognized that concentrations of 1–2 ng/ml were the minimum therapeutic level “accepted by the opinion leaders in the field.” DTX-010.0002.

D. Alkermes’s attacks against the Depotrex prior art fail

Teva expects Alkermes will argue that the Depotrex-related prior art cannot invalidate the asserted claims because: (a) it purportedly does not teach administering the claimed dose or achieving the claimed AUC properties with that dose; and (b) the Depotrex product cannot qualify as prior art. These assertions are meritless.

Alkermes has pointed to Dr. Comer’s administering the 384-mg dose of Depotrex in two 192-mg injections into each buttock during the same procedure as failing to teach the claimed “step of parenterally administering” the claimed dose, because it was not given in a “single injection.” But the claims on their face refer only to an “administration” step and do not require a “single injection.” Nor does the specification foreclose carrying out the administration step by multiple injections.⁴ What matters in the context of this patent is that the patient receive the claimed dose, not whether the injected dose comes in one shot or two, or whether the oral dose comes in one pill or two. *Brookhill-Wilk I, LLC v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1298 (Fed. Cir. 2003) (“the analytical focus must begin and remain centered on the language of the claims themselves”); *Falana v. Kent State Univ.*, 669 F.3d 1349, 1355 (Fed. Cir. 2012) (“[a]

⁴ Dr. Ehrich’s discussion in his declaration to the Patent Office regarding a “single 380 mg injection” of the formulation, DTX-002.0493, also does not show that the claims should be limited to a single injection: the law is clear that importing a limitation from the file history that is inconsistent with the plain language of the claims and the specification is improper. *Baxalta Inc. v. Genentech, Inc.*, 972 F.3d 1341, 1346–49 (Fed. Cir. 2020) (construction based on statements made during prosecution “incorrect” where it was “inconsistent with the plain language of the claims and [the specification]”). Indeed, the file history as a whole confirms that limiting the administration step to a single injection is improper: in its decision to institute the IPR against the ’499 patent, the PTAB found that Comer’s disclosure of two injections totaling 384 mg taught the administration step of the claims. DTX-002.0798.

court may not import limitations [] into the claims.”).

Any suggestion that the 384-mg dose of Depotrex does not inherently result in an AUC that is about three times higher than the AUC of 50 mg/day of oral naltrexone is also wrong. Comer and Nuwayser show precisely the claimed AUC properties stemming from administration of the 384-mg dose of Depotrex (when applying the inventor’s AUC methodology to Comer’s and Nuwayser’s naltrexone blood concentration data). *Supra*. Indeed, the *only* evidence Alkermes has cited to show the claimed AUC properties are not inherent to administration of the 384-mg dose of Depotrex is the fact that a *different* prior-art formulation that used a *different* polymer (PLA instead of PLGA) allegedly did not exhibit such properties. DTX-002.0494 (citing Tice, DTX-137); D.I. 165 at 41–42 (same). But the fact that a different delivery system yields different results does not diminish the fact that the claimed PLGA delivery system, also used in Depotrex, inherently yields the claimed results.

Alkermes has argued that the Depotrex product is not prior art at all because it was “secret” and its properties were not known. Depotrex was clearly not a secret as it was extensively described in public documents and used in clinical trials dated well before the ’499 patent. Kerrigan Tr. Vol. 2 at 56:10–22. And the properties of a prior-art product can be proven with evidence that is not itself prior art (as when one conducts tests on the product after the relevant priority date). *Hospira*, 946 F.3d at 1329–30. The evidence of Depotrex’s properties comes largely from a former BioTek employee who worked with Depotrex, James Kerrigan. His testimony regarding the composition and AUC properties of Depotrex is corroborated by and fully consistent with the public disclosures within the various papers and patents regarding Depotrex, described above. *Supra*. Moreover, even if Depotrex is found not to be prior art, it is still “persuasive evidence” that creating a long-acting naltrexone-PLGA formulation in the

claimed dose and achieving the claimed AUC “was the product only of ordinary [] skill.” *Geo M. Martin Co. v. All. Machine Sys. Int’l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010).

III. Alkermes’s secondary considerations of non-obviousness are insufficient to overcome Teva’s strong *prima facie* case of obviousness

Given the stark similarity between the prior art and Alkermes’s asserted claims, Alkermes heavily relies upon so-called secondary considerations of non-obviousness for its Vivitrol product. Alkermes’s reliance is unavailing. *First*, while such secondary evidence must be considered, it cannot override a strong *prima facie* showing of obviousness. *Adapt*, 25 F.4th at 1372. Thus, since the claimed invention “represent[s] no more than the predictable use of prior art elements according to their established functions,” Alkermes’s secondary evidence is “inadequate to establish non-obviousness as a matter of law.” *Stone Strong, LLC v. Del Zotto Prods. of Fl., Inc.*, 455 F. App’x 964, 971 (Fed. Cir. 2011) (citing *KSR*, 550 U.S. at 417).

Second, the burden is on Alkermes to establish “a nexus between the evidence [of secondary considerations] and the merits of the claimed invention.” *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010). But Alkermes cannot establish such a nexus. For starters, while there is a rebuttable presumption of nexus if Alkermes can show that its evidence “is tied to a specific product and that product embodies the claimed features, and is coextensive with them,” such a presumption does not apply where that product is also covered by additional, separate patents. *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373, 1375 (Fed. Cir. 2019). Here, Vivitrol encompasses the additional, unclaimed Medisorb PLGA drug delivery technology that was claimed in at least eighteen other patents unrelated to the ’499 patent. DTX-174.0977. Thus, the burden remains on Alkermes to show that its secondary evidence regarding Vivitrol has a nexus to the claimed invention. *Teva Pharms. Int’l GmbH v. Eli Lilly & Co.*, 8 F.4th 1349, 1360 (Fed. Cir. 2021).

Additionally, regardless of whether Alkermes can show that there is a presumption of nexus (it cannot), Alkermes's secondary considerations evidence is not relevant to obviousness because such evidence is attributable to extraneous factors other than the merits of the patented invention, as explained below. *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

A. Vivitrol did not satisfy any relevant long-felt but unmet need for a long-acting naltrexone product, and there was no related failure of others

Alkermes contends there was a long-felt but unmet need for a safe and effective long-acting naltrexone formulation that Vivitrol allegedly satisfied. Alkermes also asserts that others failed to develop such a formulation. Not so. Depotrex previously succeeded in meeting the need for any such formulation. *Geo. M. Martin Co. v. All. Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1304–05 (Fed. Cir. 2010) (no evidence of long-felt need or failure of others given minimal differences between prior art and the claimed invention); *In re PepperBall Techs., Inc.*, 469 F. App'x 878, 882–83 (Fed. Cir. 2012) (no long-felt need as “others had previously solved the [] need”).

Alkermes's only rebuttal is that Depotrex was not FDA approved, and so there was still a long-felt but unmet need for an *FDA-approved* long-acting naltrexone formulation. Alkermes is wrong as a matter of law. Nothing in the asserted claims requires FDA approval, and the requirements for FDA approval differ from and are irrelevant to the requirements for patentability. *In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995) (“FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws”); *Amarin Pharma, Inc. v. Hikma Pharms. USA Inc.*, 449 F. Supp. 3d 967, 1006 (D. Nev. 2020) (citing *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013)) (difficulties that a prior-art product may have in receiving FDA approval “are not particularly probative” to non-obviousness “because there is no requirement [of] a reasonable expectation of success in developing” an FDA-approved product). Thus, the Federal Circuit has held that the mere fact that a prior-art

product was not FDA approved is not probative of non-obviousness so long as the treatment was already known in the art. *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1331 (Fed. Cir. 2017) (“fact that [patentee] was the first to receive FDA approval . . . does not overcome the fact that [the treatment was] already known”); *Adapt*, 25 F.4th at 1376–77 (similar).

Further, the evidence shows the reason that Depotrex was not ultimately FDA-approved was not due to technical issues—instead, it was extensively tested and found to be safe and effective—but rather because BioTek simply lacked the finances to continue the regulatory approval process. Kerrigan Tr. Vol. 2 at 128:10–129:1. Depotrex’s lack of FDA approval is thus irrelevant to non-obviousness for this separate reason. *Cubist Pharms., Inc. v. Hospira, Inc.*, 805 F.3d 1112, 1126 (Fed. Cir. 2015) (prior product’s failure to reach market irrelevant because it was caused by “economic considerations” rather than “difficulties in the lab”).

B. No skepticism regarding desirability of long-acting naltrexone product

To the extent that Alkermes argues that there was skepticism regarding the desirability of a long-acting naltrexone formulation like the one claimed, Alkermes is wrong for the same reasons discussed above with respect to teaching away. *See* Section II.C, *supra*. Moreover, the relevant consideration for skepticism is whether there was skepticism that the invention would work as intended, yet Alkermes has cited no evidence that the industry was skeptical that administering claimed dosage of long-acting naltrexone would result in the claimed AUC profile. *Dow Jones & Co. v. Abblaise Ltd.*, 606 F.3d 1338, 1352 (Fed. Cir. 2010). To the extent Alkermes points to Vivitrol’s initial low revenues following launch as evidence of industry skepticism, this is irrelevant to non-obviousness since Alkermes failed to provide any evidence that these low revenues were due to skepticism about the claimed AUC properties of the claimed invention, as opposed to other factors. *Kroy IP Holdings, LLC v. Safeway, Inc.*, 107 F. Supp. 3d 656, 676–77 (E.D. Tex. May 29, 2015), *aff’d*, 639 F. App’x 637 (Fed. Cir. 2016) (difficulty commercializing

patented product not relevant to skepticism because it was “likely” that the industry regarded the invention “as not having broken new ground” and thus was not “worthy of licensing”).

C. There were no unexpected results as compared to the closest prior art

Alkermes focuses the entirety of its unexpected results assertions on the alleged benefits the 380-mg dose of Vivitrol has over oral naltrexone, other addiction treatments, and other doses of long-acting naltrexone formulations, such as a 190-mg dose. However, the relevant questions for unexpected results are whether a person of ordinary skill in the art would have expected the beneficial properties of the claimed invention as compared to the closest prior art, and whether any differences are simply a matter of degree rather than in kind. *Abbott Labs v. Andrx Pharms., Inc.*, 452 F.3d 1331, 1345 (Fed. Cir. 2006); *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). Here, the closest Depotrex-related prior art teaches a skilled artisan to expect that administering a long-acting naltrexone-PLGA formulation in the claimed dose will result in the recited AUC properties and effective treatment. Similarly, any differences between Depotrex and the claimed invention are plainly not differences in kind, as the administration of Depotrex provides effectively identical results as the claimed invention.

D. Evidence of praise is unrelated to the merits of the claimed invention

Alkermes’s evidence of industry praise for Vivitrol should be accorded little weight as it is not attributable to the AUC features of the claimed invention. *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 838 (Fed. Cir. 2015). Instead, the praise cited by Alkermes relates to features that were well known in the prior art, such as the efficacy of naltrexone and the patient-compliance benefits stemming from a long-acting formulation, which is insufficient to establish relevant praise. *Id.*; see also *ClassCo, Inc. v. Apple, Inc.*, 838 F.3d 1214, 1220 (Fed. Cir. 2016).

E. Any commercial success of Vivitrol is unrelated to the merits of the claimed invention

Although Alkermes realized profits from sales of Vivitrol, any commercial success of Vivitrol is not attributable to the merits of the claimed invention and is therefore irrelevant to non-obviousness. *Geo M. Martin*, 618 F.3d at 1304; *Ormco*, 463 F.3d at 1311–12. First, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] *In re DBC*, 545 F.3d 1373, 1384 (Fed. Cir. 2008) (commercial success due to promotional efforts rather than the unique features of the claimed invention not pertinent to non-obviousness). [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] *Sanofi-Aventis Deutschland GMBH v. Mylan Pharms. Inc.*, 791 Fed. App'x 916, 927 (Fed. Cir. 2019) (the fact that a prior version of the patentee's product without the claimed features exhibited significant commercial success and was still on the market "would suggest that the success [of the patented invention] is not traceable" to the merits of the claims).

F. Teva's ANDA filing does not show copying or any other objective indicia that is probative of non-obviousness

Alkermes contends that Teva's decision to file its ANDA is evidence of copying and other objective indicia of non-obviousness, like long-felt, unmet need and commercial success. It is not. As explained in Teva's motion *in limine* (D.I. 164), the Federal Circuit recognizes that a generic's decision to file an ANDA is irrelevant to these issues. *See id.* at 1–3.

IV. If the recited AUC properties are not inherent, then the asserted claims are invalid for lack of written description

Alkermes may attempt to avoid the strong case of obviousness by asserting that

administration of the 384-mg dose of Depotrex would not inherently result in the recited AUC properties of the claims. While Alkermes is wrong, *supra* Section II.D, to the extent that achievement of the recited AUC properties is *not* deemed to be an inherent property of administering such a formulation, then the claims are invalid because Alkermes failed to provide the legally required support for the AUC limitations.

Specifically, in exchange for the patent monopoly, 35 U.S.C. § 112 requires the patentee to describe the invention “in such terms that any person skilled in the art [] may construct and use it after the expiration of the patent.” *Permutit Co. v. Graver Corp.*, 284 U.S. 52, 60 (1931). Thus, “section 112 has been construed to mandate that the specification” must, *inter alia*, “describe the invention sufficiently to convey to a person of skill in the art that the patentee had possession of the claimed invention at the time of the application, i.e., that the patentee invented what is claimed. [written description requirement.]” *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1344–45 (Fed. Cir. 2005). If the AUC limitations are deemed *not* to be an inherent result of administering a long-acting naltrexone-PLGA formulation in the claimed dose, then the ’499 patent specification fails this written description requirement.

First, the asserted claims broadly cover the use of *any* PLGA delivery system within the claimed formulation that achieves the claimed AUC results. Yet the specification provides only a *single* working example of the use of a *single* specific PLGA delivery system to achieve the claimed AUC results—Alkermes’s Medisorb polymer. DTX-001.0009–0016 at 5:35–8:2. If the claimed AUC profile is not an inherent feature of naltrexone-PLGA formulations, then the patent fails to show that Dr. Ehrich possessed the capability to achieve the claimed AUC profile using polymers other than Medisorb. *LizardTech*, 424 F.3d at 1346 (claims lacked written description where the specification described only one mode of compressing an image but the claims

encompassed all modes that could compress an image); *Lipocine Inc. v. Clarus Therapeutics, Inc.*, 541 F. Supp. 3d 435, 446, 451 (D. Del. 2021) (claims broadly covering a “long list [] of formulations” that achieved certain properties lacked written description where “with very few exceptions, the specification does not identify which” provided those properties).

Second, and more fundamentally, the specification also fails to show that Dr. Ehrich was in possession of *any* long-acting naltrexone-PLGA formulation that achieves the recited AUC properties, as it fails to present any AUC data at all. Instead, the specification simply makes the bare, unsupported assertion that the formulation achieved the claimed AUC. DTX-001.0007 at 1:30–40, 2:29–36. The law requires that written description be shown in the “four corners of the specification,” which the ’499 specification does not do. *Ariad Pharms., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351–52 (Fed. Cir. 2010); *Nuvo Pharms. (Ireland) Designated Activity Company v. Dr. Reddy’s Labs Inc.*, 923 F.3d 1368, 1381 (Fed. Cir. 2019); *In re Downing*, 754 F. Appx. 988, 995 (Fed. Cir. 2018).

CONCLUSION

For the foregoing reasons, Teva respectfully submits the Court should hold all of the asserted claims to be invalid.

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CERTIFICATE OF SERVICE

I, Mary Hogan, hereby certify that on November 1, 2022, I caused a true and correct copy of Teva's Pre-Trial Brief to be served upon all counsel of record for Plaintiffs via email.

Mary Hogan

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